CLINICAL SCIENCE

Nutritional status and lipid profile of HIV-positive children and adolescents using antiretroviral therapy

Patricia Viganó Contri,[I] Érica Miranda Berchielli,[I] Marina Hjertquist Tremeschin,[I] Bento Vidal de Moura Negrini,[I] Roberta Garcia Salomão,[I] Jacqueline Pontes Monteiro[II]

[I]Nutrition and Metabolism, Medical School of Ribeirão Preto, University of São Paulo Department of Pediatrics, Ribeirão Preto, São Paulo/Brazil. [II]Clínica Médica, Medical School of Ribeirão Preto, University of São Paulo, Ribeirão Preto, SP/Brazil.

OBJECTIVE: To describe nutritional status, body composition and lipid profile in children and adolescents receiving protease inhibitors.

METHODS: Fifty-nine patients, 23 treated with protease inhibitors (group 1) and 36 not using protease inhibitors (group 2). Their dietary intake, anthropometry, bioimpedance analysis and lipid profile variables were measured.

RESULTS: There was no difference in nutritional status or body composition between groups at the beginning of the study. After 6 months of follow-up, there was an increase in weight and height in both groups, as well as in waist circumference and subscapular skinfold thickness. In group 2, body mass index and triceps skinfold thickness adequacy were significantly higher after 6 months of follow-up. The groups had similar energy and macronutrient intake at any time point. After 6 months, group 1 had a higher cholesterol intake and group 2 had a higher fiber intake. Triglyceride serum levels were significantly different between the groups, with higher values in G1, at any time point [G1: 153 mg/dl (30–344); 138 (58–378) versus G2: 76 mg/dl (29–378); 76 (29–378)]. After 6 months of follow-up, G1 had higher LDL-cholesterol than G2 [104 mg/dl (40–142) versus 82 (42–145)].

CONCLUSION: The use of protease inhibitors, per se, does not seem to significantly interfere with anthropometric measures, body composition and food intake of HIV-infected children and adolescents. However, this antiretroviral therapy was associated with a significant increase in triglyceride and LDL-cholesterol in our subjects.

KEYWORDS: Children and adolescents; HIV; Protease inhibitor; Dyslipidemia; Nutritional status.

INTRODUCTION

Highly active antiretroviral therapy (HAART) including protease inhibitors (PI) has been associated with effective and lasting reduction in HIV viral load, with a decreased incidence of opportunistic infections and an improvement in the survival, neurodevelopment, growth and quality of life of infected children.[1,2]

Some studies have shown that the introduction of HAART results in a significant catch-up in weight and height without an increase in body mass index (BMI).[1,3,4] A report of 192 children showed that an increase in mean weight z-scores to normal values was obtained after 48 weeks and an increase in mean height z-scores approached normal values in 96 weeks after the initiation of HAART.[3] Therefore, treatment that includes PI has a positive effect on

patients' nutritional status, promoting an increase in fat mass, fat-free mass and body cell mass.[5]

However, a number of adverse effects associated with HAART, and particularly PI, such as lipodystrophy syndrome, hyperlipidemia and peripheral insulin resistance, have been identified in adult and pediatric patients.[5,6] HIV-positive children and adolescents receiving PI may be less nutritionally compromised, but may have more altered lipid profiles compared with those receiving no PI.

The pediatric literature on this issue is relatively scarce, especially in the Brazilian population. The aim of the present study was to describe, at two time points, the body composition, nutritional indicators, energy and nutrient intake and lipid profile in two clinically stable groups of HIV-positive children and adolescents using or not using PI.

METHODS AND MATERIALS

A descriptive longitudinal study was undertaken at the pediatric HIV outpatient clinics of a school hospital. Fifty-nine patients were recruited for the study and divided into two groups: HIV-positive children and adolescents using PI (group 1, n = 23) and HIV-positive children and adolescents

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not using PI (group 2, n = 36). Each group was assessed at two time points, i.e., at the beginning of the study (M1) and after 6 months of follow-up (M2). The subjects of this study were randomly selected and were paired for age and gender.

Inclusion criteria were as follows: the subjects should be between 3 and 17 years of age, should have the ability to complete anthropometry, should not be taking appetite stimulants or undergoing enteral or parenteral nutrition therapy and should be on stable treatment with HAART for at least 3 months prior to the study. Exclusion criteria were as follows: subjects who were smokers, pregnant, who had been hospitalized or developed serious illness within the 3 months prior to the beginning of the study, and who had chronic diseases such as diabetes mellitus, diarrhea, liver disease, cystic fibrosis, pancreatitis and renal failure that could interfere with the development of the child and his/her nutritional status.

Age and gender data, clinical and immunological characteristics, including lipid profile, current antiretroviral therapy, CD4 cell count, viral load and CDC clinical stage, were obtained from the medical records.[7]

Weight, height and waist circumference were assessed according to Heymsfield et al.[8] by a dietitian who was trained to take all measurements. Reference data from the World Health Organization/National Center for Health Statistics/Center for Disease Control and Prevention were used. Midarm circumference, subscapular skinfold and triceps skinfold were measured to determine lean body mass and fat mass. Fat-free mass and total body water were estimated by bioelectrical impedance using an RJL Bioelectric Impedance Analyzer® (BIA 103-A; Detroit, MI, USA).

Usual food diary for the last 3 months was assessed, and intake of energy, macronutrients, fiber, cholesterol, vitamin A and vitamin C was calculated with the DietWin® software at the two time points studied. The Dietary Reference Intake (DRI) was used to calculate the adequacy of nutrient intake.[9]

The criteria set forth in the guidelines for the prevention of atherosclerosis in childhood and adolescents were used to define abnormal lipid levels. Hypercholesterolemia was defined as a total fasting cholesterol level >170 mg/dl and a low-density lipoprotein cholesterol level >130 mg/dl. Hypertriglyceridemia was defined as a fasting triglyceride level >130 mg/dl.[10] The non-high-density lipoprotein (HDL)-cholesterol was calculated as the difference between total cholesterol and HDL-cholesterol.[11]

The study was approved by the institutional ethics committee, and all patients or their parents gave written informed consent to participate after a detailed explanation to each family.

STATISTICAL ANALYSES

Data are reported as median and range. The non-parametric Mann–Whitney test was used to compare variables with non-normal distribution. The χ^2 test or Fisher exact test was used to compare frequency distributions across groups, and the Wilcoxon test was used for longitudinal analysis. The level of significance was set at $p < 0.05$ in all analyses. Data were analyzed using the Statistical Package for the Social Sciences® (SPSS) software, version 15.0.

RESULTS

The clinical and demographic characteristics of the groups are described in Tables 1 and 2. All patients recruited were clinically stable, and the clinical, immunological and virology parameters did not differ significantly between groups at any time point. The time of using antiretroviral therapy was similar between groups (PI = 51.45 ± 31.07; non-PI = 63.97 ± 36.84 months; $p = 0.157$). Longitudinal analysis showed a significant difference in age between the groups, as expected.

Anthropometric measurements and body composition results, at the two time points, are described in Table 3. After 6 months of monitoring, weight, height, waist circumference and subscapular skinfold thickness were significantly higher in both groups. Among subjects who did not use PI, BMI and triceps skinfold thickness adequacy were significantly higher after 6 months of monitoring.

HIV-positive children and adolescents had similar daily energy intake and percentage of daily energy intake, protein, fat and carbohydrates at the two time points. After 6 months of monitoring, the group using PI had a higher cholesterol intake, and the group not using PI had a higher fiber intake. Both groups had a decrease in vitamin A intake after 6 months of monitoring. Vitamin C intake was lower after 6 months of monitoring only in the non-PI group (Table 4).

Serum triglyceride levels and non-HDL-cholesterol levels were significantly higher in the PI group compared with the non-PI group, at any time point. The proportion of patients with hypertriglyceridemia was significantly higher in the PI group compared with the non-PI group at the two time points (M1: PI 39% versus non-PI 2.7%; $p = 0.0003$; M2: PI 34.6% versus non-PI 8.3%; $p = 0.01$). Total cholesterol and HDL-cholesterol did not differ significantly between groups, whereas serum LDL–cholesterol levels were higher in subjects using PI, but only after 6 months of follow-up (Table 5).

DISCUSSION

In the present study, HIV-infected children and adolescents presented similar anthropometric measurements, food intake and body composition measurements regardless of antiretroviral therapy. Serum triglyceride and LDL-cholesterol levels were higher in the PI group than in the non-PI group.

Over the last few years, numerous advances in antiretroviral therapy have resulted in the improved survival and nutritional status of individuals with HIV.[2] Progress in the treatment of AIDS has changed it into a chronic disease. Clinical and immunological progression of the disease was not observed in any of the subjects evaluated in the present study.

In agreement with the results of Melvin et al.,[12] children and adolescents receiving PI therapy in the present study had clinical characteristics consistent with more advanced disease.

In this study, children and adolescents were similar regarding nutritional status at the two time points. After longitudinal analysis, a statistically significant increase in BMI and triceps skinfold thickness was only observed in the non-PI group. Studies have corroborated our results and have shown nutritional status deterioration in children using protease inhibitors. Dzwonek et al.[13] found a

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Table 1 - Clinical and demographic characteristics of HIV-positive children and adolescents using and not using PI: analysis between groups and longitudinal analysis.

Parameters	G1 (PI)		G2 (No IP)	
	M1	M2	M1	M2
Age (months)	114 (54–196)	121* (59–201)	110 (60–190)	118† (66–195)
% Female	60.9	60.9	44.4	44.4
T-CD4$_+$ lymphocyte count (cell/mm^3)‡	565 (74–1925)	613 (31–1983)	686.5 (240–1533)	727 (192–13.800)
Viral load (copies/ml)‡	9474.5 (<50–47.088)	3329.5 (<50–282.247)	7846 (<50–96.886)	7600 (<50–160.069)

G1: group using PI; G2: group not using PI.
M1: initial moment; M2: final moment.
*Values were statistically different in the group of children and adolescents using PI (G1) after 6 months of follow-up: $p < 0.05$.
†Values were statistically different in the group of children and adolescents not using PI (G2) after 6 months of follow-up: $p < 0.05$.
‡Values were not statistically different between groups of children and adolescents using and not using PI and in longitudinal analysis: $p > 0.05$.

reduction in body weight, BMI, mid-upper arm circumference and subcutaneous fat in children using protease inhibitors.

Fiore et al.[5] and Melvin et al.[12] did not find any differences in body composition or in anthropometric indices between groups using PI or not, the same as in the present study. Some studies have shown gain in fat mass, lean mass and body cell mass, whereas others have found improvement in only one body compartment.[4]

Our results also suggest that the increase in waist circumference and subscapular skinfold thickness after 6 months of follow-up in both groups of children and adolescents may represent a predisposition to visceral fat accumulation.[14] Evaluation of alterations indicative of body fat redistribution in HIV-positive children is known to be difficult because of the changes in body composition that are characteristic of childhood and adolescence, and also because of the scarcity of reports in the literature.[15]

Bioelectrical impedance did not predict morphological changes in the present study. Both groups had similar and unchanged body composition. The applicability of the bioelectrical impedance prediction equations for total body water and for fat-free mass to children with specific medical problems has been questioned.[16] Other techniques could be used to better characterize the redistribution of body fat, including skinfold thickness measurements, the segmental

bioelectrical impedance technique, dual–energy X-ray absorptiometry and magnetic resonance imaging.[17]

The energy and protein consumption of most children and adolescents seemed to be adequate and was similar between the two groups at the two time points. The results are similar to those reported by Tremeschin et al.[18] Miller et al.,[19] in a large prospective study, showed that stable HIV-infected children receiving well over the recommended dietary allowance (RDA) in total calories and protein still had growth parameters below those found in the control group.

Arpadi et al.[16] suggested that the level of viral load could influence the amount of lean mass and the food intake of HIV-infected children. Thus, it is possible that viral load or aspects of the immune response, as well as the production of inflammatory cytokines, adversely affects the food intake and growth of these individuals.

Sharma et al.[20] analyzed dietary macronutrient intake in HIV-infected children for 10 years, and observed that energy intake exceeded the estimated energy requirement (EER) for ideal body weight by 62% for males and 39% for females in 1995; and in 2004, energy intake still remained 19% above the EER in both groups. They also found that protein intake was nearly 400% of the RDA for ideal body weight in 1995, and daily protein intake still exceeded the RDA by 60% in both groups in 2004.

Both groups of HIV-infected children and adolescents presented a low percentage of adequate fiber consumption and, at time point 2, the patients not using PI increased fiber consumption. Despite the apparent adequacy of vitamin A intake in both groups, at both time points, there was a statistically significant reduction in vitamin A intake after 6 months of follow-up. The same occurred with vitamin C intake, but only in the non-PI group. These events should be checked periodically in order to avoid subclinical deficiencies.

Although definitions of retinol deficiency vary across studies, reports of retinol deficiency in preschool children show rates up to 74.5% in Brazil, 30% in Argentina and 46% in Mexico.[21] This study supports the idea of poor intake as the main cause for the high prevalence of retinol deficiency.[22] Vitamin A deficiency is associated with exacerbation of oxidative stress, decrease in CD4$^+$ cells, increase in HIV-related morbidities, accelerated disease progression owing to greater activation of nuclear factor-κB and higher mortality.

Furthermore, HIV-infected patients seem to be particularly vulnerable to nutritional deficiencies that impair their already compromised immune function. These

Table 2 - Clinical category of HIV-positive children and adolescents using and not using PI: analysis between groups and longitudinal analysis.

Clinical category*	G1 (PI)		G2 (No PI)	
	M1	M2	M1	M2
	N (%)	N (%)	N (%)	N (%)
N/A: without or mild symptoms	3 (13)	3 (13)	9 (25)	9 (25)
B: moderate symptoms	5 (21.7)	4 (17.4)	9 (25)	9 (25)
C: severe symptoms	15 (65.2)	16 (69.6)	18 (50)	18 (50)

G1: group using PI; G2: group not using PI.
M1: initial moment; M2: final moment.
*Values were not statistically different between groups of children and adolescents using and not using PI and in longitudinal analysis: $p > 0.05$.

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Table 3 - nthropometric measurements and body composition by bioelectrical impedance technique of HIV children and adolescents using and not using PI: analysis between groups and longitudinal analysis.

Parameters*	G1 (PI)		G2 (No PI)	
	M1	M2	M1	M2
Weight (kg)	24.3 (15.6–48.9)	26.6† (16.8–54.9)	26.05 (14.07–62.4)	27.8‡ (15.8–61.8)
Height (cm)	129 (99–164)	131.5† (102–166.5)	126.5 (101–159)	129.1‡ (103–167.5)
BMI (kg/m^2)	16.3 (13.3–19.7)	16.2 (12.7–19.8)	16.2 (13.5–24.7)	16.6‡ (14.0–23.8)
Height/age adequacy (%)	94.3 (81.7–100.8)	95.9† (81.2–101.8)	95.8 (87.8–109.4)	96.07 (84.9–104.3)
Weight/age adequacy (%)	90.90 (58.5–113.3)	89.4 (56.3–124.8)	90.7 (61.8–138.1)	91.1 (62.6–139.2)
Weight/height (%)	100 (81.1–113.5)	100.5 (77.4–123)	100.8 (81.1–135)	98.9 (79.0–146.7)
Waist circumference (cm)	59.5 (53–76)	62† (52–76)	60 (50–81)	61‡ (52.5–84.5)
Triceps skinfold thickness (% adequacy)	72.7 (33.3–111.1)	81.8 (38.1–133.1)	77.7 (40–150)	79.8‡ (51.8–108.9)
Subscapular skinfold thickness (% adequacy)	100 (50–261.53)	111.1† (53.3–369.2)	108.3 (38.4–228.5)	121.5‡ (50–280)
Midarm circumference (cm)	15.4 (12.8–20.74)	15.3 (13.2–22.4)	15.8 (11.8–19.3)	16.1 (12.4–20.3)
Lean body mass (%)	79.7 (68.8–96.9)	79.4 (68.8–96.2)	83.6 (64–90.2)	82.6 (64.4–89.5)
Fat mass (%)	19.6 (3.06–31.1)	20.75 (3.82–31.2)	16.4 (9.9–30.5)	16.8 (10.3–35.5)
Total body water (%)	75.2 (69.6–88)	75 (70–81)	76.1 (70.1–88)	76.4 (68.8–79.1)

G1: group using PI; G2: group not using PI.
M1: initial moment; M2: final moment.
*Values were not statistically different between groups of children and adolescents using and not using PI: $p > 0.05$.
†Values were statistically different in the group of children and adolescents using PI (G1) after 6 months of follow-up: $p < 0.05$.
‡Values were statistically different in the group of children and adolescents not using PI (G2) after 6 months of follow-up: $p < 0.05$.

susceptibilities might cause intracellular dysfunction in some metabolic pathways, which in turn might inhibit growth and impair the prognosis of the disease.[23]

Hyperlipidemia has been observed as early as a few weeks after the introduction of PI in adult patients, and it is a major concern because of its association with atherosclerosis. In fact, several recent case reports described cardiovascular events in young patients taking PI and showing high levels of total cholesterol and triglycerides in the absence of other risk factors.[24] But dyslipidemia in adult HIV-positive patients can be controversial. Daminelli et al.[25] found that an HIV-positive group had smaller cholesterol and triglyceride concentrations than healthy control subjects, and HDL-cholesterol was similar in both groups.

The results of our study showed that up to 23% of subjects had abnormal lipid levels. The predominant lipid abnormality associated with PI treatment is hypertriglyceridemia. This finding is similar to what has been demonstrated in other studies in which individuals using PI had higher triglyceride levels than those not using PI.[5,6] Other studies

of HIV-infected adults treated with PI obtained the same results.[26,27]

Several small cross-sectional studies have shown elevations in total cholesterol in HIV-infected children.[6] In contrast, in the present study, serum LDL-cholesterol levels were increased after 6 months of monitoring in the PI group, but these values were close to the normal levels recommended, and might be a reflection of a higher cholesterol intake after 6 months of monitoring. Chantry et al.,[28] evaluating the lipid profile and glucose homeostasis in HIV-positive children after initiating or changing antiretroviral therapy, found that 99% of the sample had higher mean saturated fat intake than recommended levels and, approximately one third of the children had a mean cholesterol intake >300 mg.

Carter et al.,[29] evaluating the cumulative risk of exposure to HAART therapy and dyslipidemia, found that an increased linear relationship between median cholesterol and duration of first PI-inclusive regimen did not persist after 24 months on the regimen. After 24 months, median

Table 4 - nergy and nutrient intake of HIV-positive children and adolescents using and not using PI: analysis between groups and longitudinal analysis.

Parameters*	G1 (PI)		G2 (No PI)	
	M1	M2	M1	M2
Energy (% adequacy)	130.12 (96.3–224.7)	134.1 (65.13–327.5)	119.3 (54.8–347.5)	136.1 (83.7–286.2)
Protein (% VET)	283.8 (144.1–538.2)	316.6 (110.3–159.5)	309.8 (88.7–834.6)	281.5 (122.7–1468)
Carbohydrate (% VET)	57.7 (31.3–69.6)	57.7 (46.1–67.7)	57.7 (43.3–223.9)	57.2 (36–298.8)
Fat (% VET)	25.6 (17.5–35.7)	25.4 (19.4–56.7)	25.3 (15.3–38.7)	25 (14.3–54.7)
Cholesterol (mg)	174.8 (115.1–360.6)	204.5† (86.3–459)	164.6 (5.4–923.77)	194.5 (43.5–682.0)
Fiber (%)	68.4 (39.3–176)	87.4 (26.1–341.7)	70.1 (11.2–205.5)	81.1‡ (33.7– 302.6)
Vitamin A (%)	141.6 (21.7–603.8)	112.16† (21.4–545.4)	145.9 (9.51–128.06)	86.07‡ (10.33–131.4)
Vitamin C (%)	209.4 (15.9–529)	135.1 (3.64–690.3)	198.7 (4.8–403.05)	112‡ (958–175.6)

G1: group using PI; G2: group not using PI.
M1: initial moment; M2: final moment.
*Values were not statistically different between groups of children and adolescents using and not using PI: $p > 0.05$.
†Values were statistically different in the group of children and adolescents using PI (G1) after 6 months of follow-up: $p < 0.05$.
‡Values were statistically different in the group of children and adolescents not using PI (G2) after 6 months of follow-up: $p < 0.05$.

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Table 5 - Lipid profile of HIV-positive children and adolescents using and not using PI: analysis between groups and longitudinal analysis.

Lipid profile	G1 (PI)		G2 (No PI)	
	M1	M2	M1	M2
Triglycerides* (mg/dl)	153 (30–344)	138 (58–378)	76 (29–378)	76 (29–378)
Cholesterol (mg/dl)	161 (87–230)	161 (87–225)	142 (98–210)	142 (91–210)
HDL-cholesterol (mg/dl)	37 (14–76)	40 (14–52)	39 (30–59)	40 (30–52)
Non-HDL-cholesterol* (mg/dl)	122 (98–170)	119 (63–170)	93 (61–125)	89 (58–161)
LDL-cholesterol (mg/dl)	91 (40–123)	104† (40–142)	82 (47–121)	82 (42–145)

G1: group using PI; G2: group not using PI.
M1: initial moment; M2: final moment.
HDL: high density lipoprotein; LDL: low density lipoprotein.
*Values were statistically different between groups of children and adolescents using and not using PI at both M1 and M2: $p < 0.05$.
†Values were statistically different between groups of children and adolescents using and not using PI only at M2: $p < 0.05$.

cholesterol remained fairly constant. Although HDL-cholesterol has not been frequently measured in HIV-infected children, Beregszaszi et al.[30] found a significant proportion of children (19%) with low HDL-cholesterol values. The present study failed to demonstrate abnormal serum levels of HDL-cholesterol.

Some studies have shown that the dyslipidemia might reflect a subclinical alteration in adipose tissue and may allow the detection of patients who are at risk of developing lipodystrophy.[31,32] Cheseaux et al.[33] concluded that HIV-infected children treated with HAART had some elevation in their cholesterol similar to that seen in patients heterozygous for familial hypercholesterolemia, and therefore have a similar risk for premature atherosclerotic disease.

The non-HDL-cholesterol levels in the plasma correlate directly with the risk of developing coronary artery disease. McGill et al.[34] showed an association between the concentrations of non-HDL-cholesterol and the extent of fatty streaks in the abdominal aorta, right coronary artery and left descending artery in adolescents and young adults.

Charakida et al.,[35] with the purpose of determining the impact of HIV infection and antiretroviral therapy on markers of early vascular disease in children, showed that HIV infection in childhood is associated with adverse structural and functional vascular changes that are most pronounced in children exposed to PI therapy. In this study, triglycerides and non-HDL-cholesterol were higher in PI-treated children compared with non-PI-treated and untreated HIV-infected children.

Although the incidence of malnutrition in children with HIV infection has decreased with HAART, a large number of patients presented the side-effects of this therapy. Dyslipidemia may develop early in children and adolescents, seems to be associated with drug dosing and may be more pronounced in children with higher PI levels.

A limitation of this study is that we did not assess the pubertal status and physical abnormalities of lipodystrophy because assessment of such abnormalities by physical examination is inherently subjective and the results may vary among different examiners.

CONCLUSIONS

In conclusion, it seems that the use of PI, per se, does not significantly improve anthropometric measures, body composition and food intake of HIV-infected children and adolescents. However, this antiretroviral therapy was associated with a significant increase in triglyceride and LDL-cholesterol levels in the subjects studied. Long-term investigations with large samples need to be conducted not only to ensure that the weight and height of these children and adolescents can be maintained at the same rate as in uninfected children, but also to evaluate the adverse effects of PI use on lipid profile.

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